WHY GUIDELINES ON TETANUS VACCINATION IN PREGNANCY SHOULD BE REVIEWED

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Presenter;

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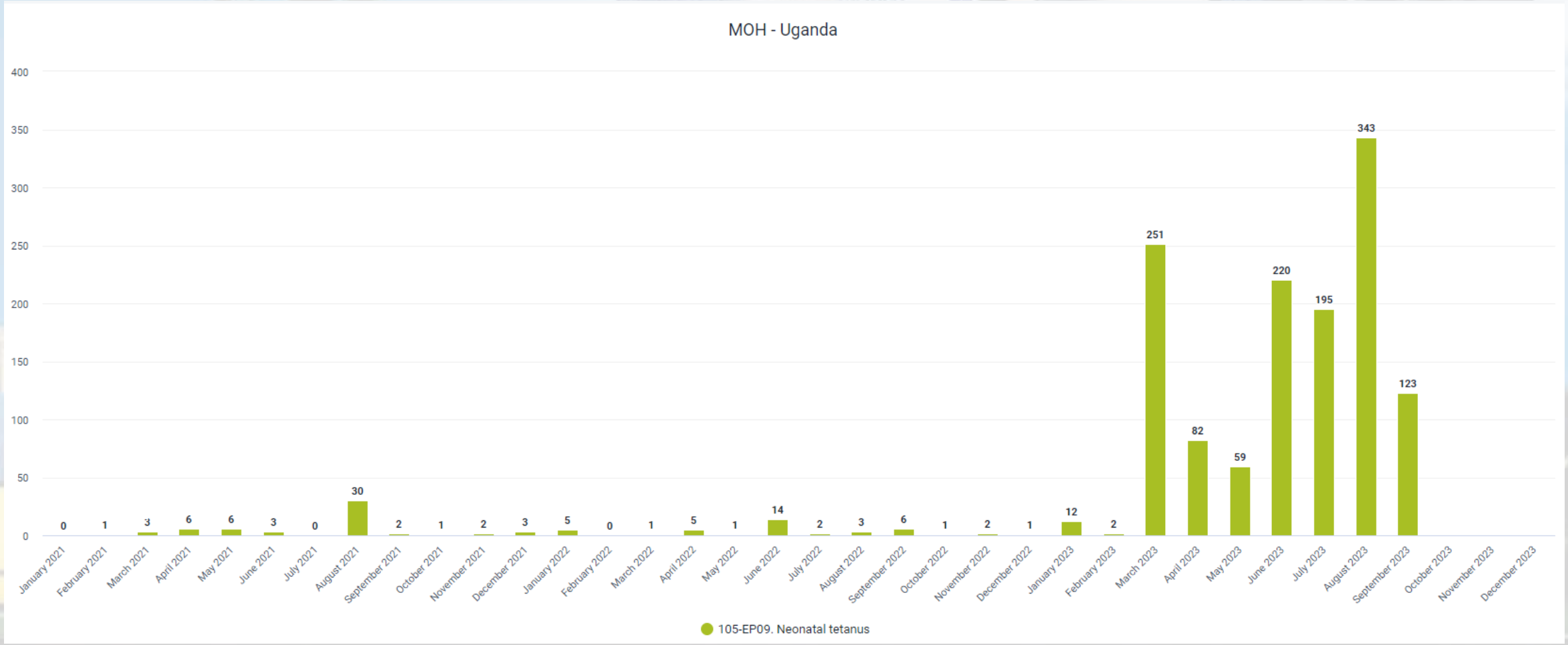
BACKGROUND

- **Neonatal mortality due to tetanus remains a cause of preventable mortality in Uganda despite the 81% TD vaccination coverage.**
- **It is a silent killer : WHO 2019**
- **The efficiency of antibody transfer is low until 32-34 WOA (Chu & Englund, 2014)**
- **Maternal antibodies are estimated to wane within a year. (Liang et al., 2018)**
- **Uganda's 2022 maternal Td vaccination guidelines contradict the other guidelines which recommend vaccination between 27-36WOA.**
- **To sustain the elimination, there in need to improve the current practices.**
- **We aimed to determine prevalence and factors associated with transfer of protective levels of anti-tetanus antibodies among newborns.**

Uganda's 2022 Td Maternal Vaccination Guidelines

	TRIMESTER	GOAL	TIMING OF CONTACT	HISTORY TAKING	EXAMINATION	LABORATORY Investigations	PROMOTION	ACTION
FIRST CONTACT	First Trimester 0 – 12 weeks	-Confirm pregnancy -General/Risk Assessment -Health Education -Plan for delivery -Appropriate preventive Interventions -Involve the male partner spouse	Contact 1: Anytime ≤12 weeks	-Presenting complaint -LNMP -Estimate period of gestation -Contraceptive? -Obstetric -Medical -Surgical -STI -Social: smoking alcohol/drugs -TB screening -Intimate Partner Violence (IPV) - Dietary	-General exam -Vital exam (e.g. BP, pulse) -SFH measurement -Abdominal/specific exam -Vulva exam (Speculum if indicated) -Nutritional assessment (height, weight, MUAC)	-Hb (CBC where available) -HIV test -Syphilis test (RPR) -Blood group/RhD -Urine albumen, Glucose -Gram staining for ASB, urine culture if indicated - Glucose tolerance test (GTT) (for suspicious cases/hospital) -RDT for Malaria (where indicated) -Hepatitis B test	-H/E on common pregnancy complaints -Address any problem -Involve husband in ANC -Draw up a birth and emergency preparedness plan -Counsel on PPFP methods -Danger Signs (abdominal pain, severe headache, blurred vision etc) -eMTCT -Nutrition education, Hygiene, Rest and exercise -Infant feeding -LLINS, IPTp use -Dangers of smoking, alcohol and substance abuse	-Tetanus/Diphtheria vaccine (Td) -Ferrous SO_4 -Folic acid -Treat incidental ailments -Condom use for HIV prevention in discordant couples and those at high risk -Debriefing mother on findings and course of action -Give next appointment and explain what will be done emphasising need to come back any time if there is need
2nd and 3rd Contact	Second Trimester **>13 – 28 weeks**	-Respond to abnormal Lab results -Provide preventive measures (Td, IPTp) -Exclude multiple pregnancy and fetal abnormalities -Promote nutrition and wellbeing -Assess for danger signs of Pregnancy Induced Hypertension and any other danger signs -Rule out anaemia	Contact 2: 13 – 20 Weeks Contact 3: 21 – 28 Weeks	-Ask for presenting complaints -Date of 1st foetal movements -vaginal bleeding -Social: smoking alcohol/drugs -TB screening -Intimate partner violence	-General exam -BP -SFH (symphysis Fundal Height) -Abdominal exam -rule out multiple -pregnancy -Nutritional assessment -Early Ultra Sound Scan best at 20 weeks but can be done up to 24 weeks	-Hb at 26 weeks -If BP ≥140/90 -Urine albumen, if there is glycosuria refer to hospital for GTT	-Address presenting complaints -Discuss Laboratory results and need to treat partner where necessary -Symptoms of PIH, vaginal bleeding -eMTCT/HCT -LLINs/IPTp use -Danger Signs -Nutrition & Hygiene, Rest and exercise -Male Involvement -Birth and emergency preparedness plan	-Td -Ferrous SO_4 -Folic acid -IPT dose -Mebendazole -Treat incidental ailments -Use of condoms in high risk individuals/ discordant -Debriefing mother -Give next appointment and explain what will be done emphasising need to come back any time if there is need

Monthly trends for neonatal tetanus



METHODS

- **Study design:** cross-sectional
- **Study Population:** 293 mother-newborn pairs at Kawempe National Referral Hospital
- **Study Duration:** 1st February to 31st March 2020
- **Procedures;**
  - At delivery, neonatal cord and maternal venous blood were collected
  - Transported to MakCHS Immunology Lab
  - Titers for anti-tetanus antibodies done using a commercial quantitative ELISA kit.
- **Data Analysis:** Study primary outcome was the proportion of newborn babies with tetanus antibodies ≥0.1 IU/mL.
- Associated factors were determined using generalized linear model for the Poisson family with a log link and robust variance estimation.

High Maternal – Neonate Transfer of Tetanus Antibodies

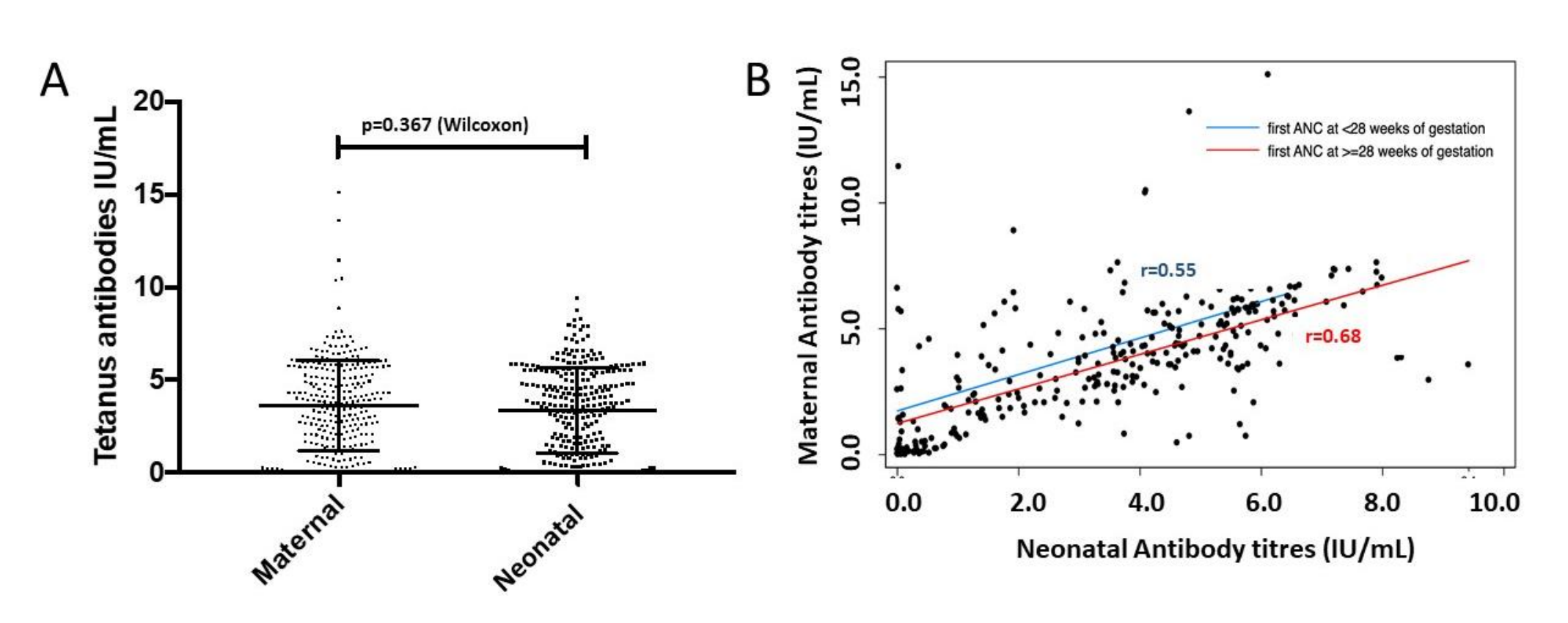
- The mean antibody titers were;
  - maternal 3.63±2.43 IU/mL
  - neonatal 3.37±2.32 IU/mL

  } no different (p=0.367, Wilcoxon) between them

  - Maternal Td antibody levels determine transfer to infant
- Prevalence of protective levels of anti-tetanus antibody titers;
  - mothers 93.9% (95% CI, 90.5 – 96.3)
  - neonates 88.1 (95% CI: 83.8-91.3)

  } no different (p=0.367, Wilcoxon) between them

No significant Difference Maternal and Neonatal levels of Tetanus antibodies & they strongly correlate



- Meaning that mothers can only transfer as much as they have
- Observation supported with a strong positive correlation between antibody levels of mother baby pairs i.e high maternal antibodies=high neonate antibodies and vice versa

Factors that determine maternal-to-neonate antibody transfer

Timing, timing, timing of the shot; It matters a lot

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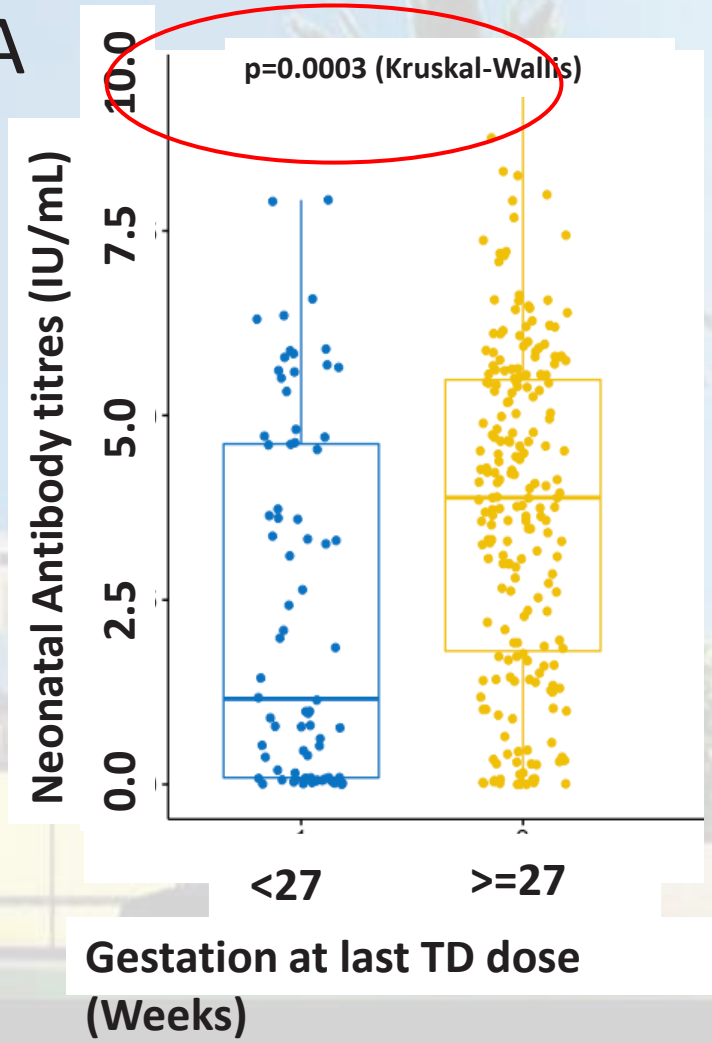
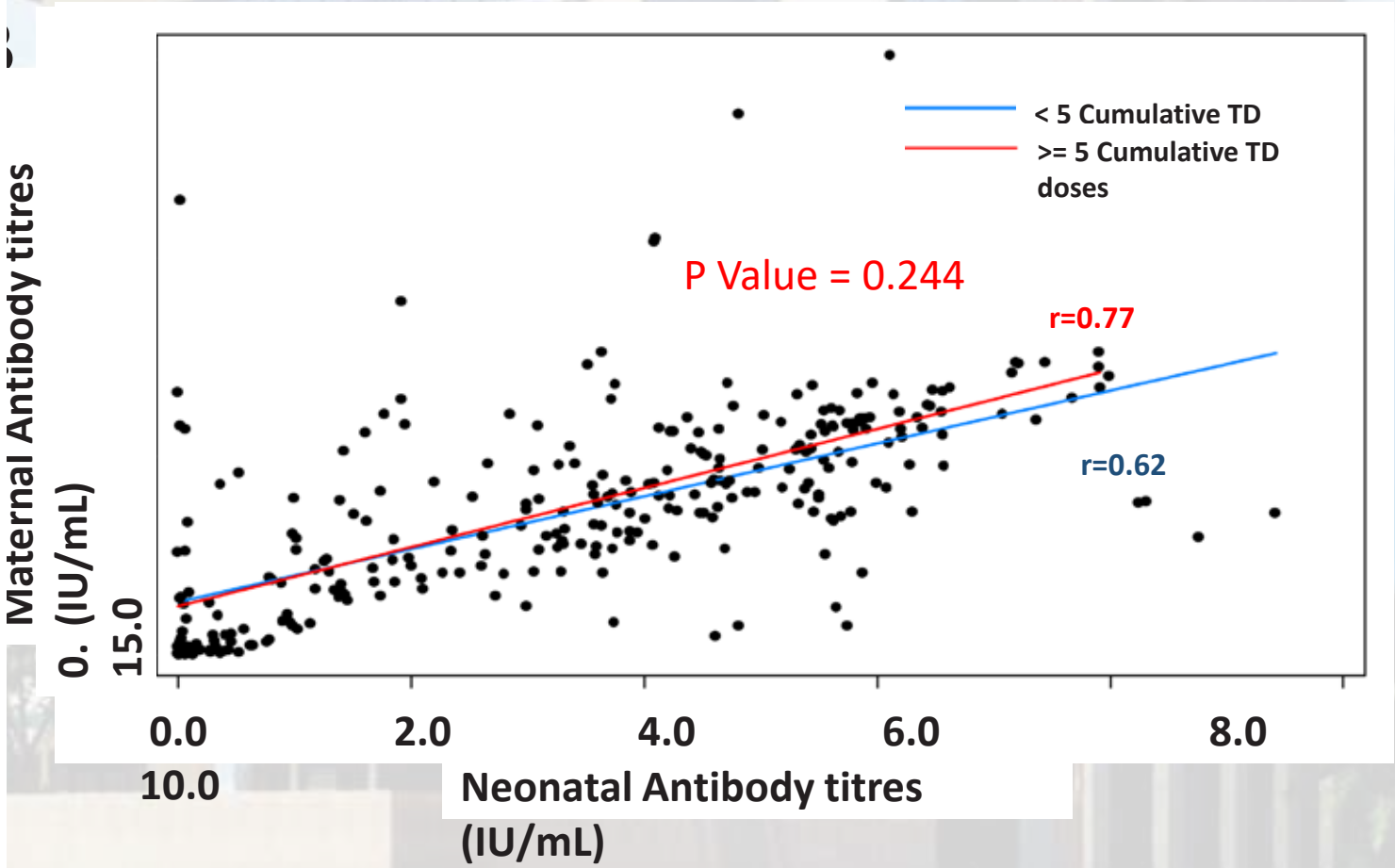


- Late ANC attendance, sometimes past 28 weeks of gestation, is prevalent in public ANC facilities
- This translates into a TdT dose being given late in gestation.
  - Is remaining time adequate to transfer adequate protective levels of antibodies??
- Neonates of mothers, recipients of ≥27 weeks TdT dose(s) had significantly higher antibodies than < 27 weeks Td dose
- ACIP recommends mothers receive a TdT dose at 27 weeks but before 36 weeks of gestation

The Paradigm of the 5 Td shots in women of Child-Bearing age; Do they still matter??

- No difference in Transfer of antibodies between mother of ≥ 5 and < 5 Td Shots



Factors associated with transfer of protective tetanus antibodies to the new born

	Variable	Crude PR	Adjusted PR	95% CI	P value
Maternal Td Titers	<0.1	1	1		
	>=0.1	3.3 (1.6-7.0)	3.1	1.5-6.4	0.002
Gestation at last TD dose	<27 Weeks	1	1		
	>=27 Weeks	1.3 (1.1-1.5)	1.1	1.0-1.3	0.034
TT/TD doses during current pregnancy	0-1	1	1		
	2	1.2 (1.1-1.3)	1.1	1.0-1.2	0.025
	3-4	1.3 (1.2-1.4)	1.1	1.0-1.2	0.004
Maternal Age	<=20	1	1		
	21-30	1.1 (0.97-1.3)	1.1	0.95-1.2	0.259
	>30	1.0 (0.88-1.2)	1.0	0.86-1.2	0.865
HIV	No	1	1		
	Yes	0.94 (0.80-1.1)	1.0	0.92-1.17	0.555
TT/TD doses before current pregnancy	<5 doses	1	1		
	>=5doses	0.94 (0.84-1.1)	0.94	0.85-1.0	0.244

CONCLUSION

- High rates of maternal-neonate transfer of protective tetanus antibodies
- Td shot at ≥27-36 weeks of gestation offers best transfer of protective antibodies
- A Td Shot required for each pregnancy irrespective of number of previous Shots

RECOMMENDATIONS

- Conduct a study with a larger sample size to ascertain the ideal timing for Td immunization during pregnancy.
- Also, the notion that accumulate of five or more Td doses accords life time protection against tetanus infection should be discarded
- mothers should be given a Td vaccination at every pregnancy.

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Antitetanus toxoid antibodies in mothers and neonates: a single-centre study from Uganda

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ABSTRACT

Background Neonatal mortality due to tetanus persists in Uganda despite the mandatory vaccination of pregnant mothers. Maternal antibodies wane within a year. Uganda's maternal vaccination guidelines do not specify the timing or frequency of tetanus shots, contributing to suboptimal transfer of tetanus antibodies to neonates. We aimed to determine the prevalence and factors associated with protective tetanus antibodies among newborns at Kawempe National Referral Hospital.

Methods We conducted a cross-sectional study among 293 mother-newborn pairs. At delivery, neonatal cord and maternal venous blood were collected and titred for antitetanus antibodies using a quantitative ELISA kit. The primary outcome of the study was the proportion of newborn babies with tetanus antibodies ≥0.1 IU/mL. Associated factors were determined using generalised linear models for the Poisson family with a log link and robust variance estimation.

Results A total of 258/293 (88.1%) newborns had protective antibody titres. Factors associated with adequate protective antibodies in the newborn included: high (≥0.1 IU/mL) maternal antibody titres, first antenatal visit ≥12 weeks of gestation and receiving a tetanus toxoid (TT) shot ≥28 weeks of gestation. However, number of doses received before current pregnancy was not associated with adequate protective antibody titres.

Conclusion There is a high prevalence of adequate protective levels of antibodies among TT-vaccinated mothers. Maternal titres and a third trimester TT dose correlate with adequate levels of protective anti-TT antibodies among newborns. A third trimester TT dose is recommended.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In tetanus-endemic regions including sub-Saharan Africa, mortality due to neonatal tetanus is 80%–100%.
⇒ Uganda gives up to five doses of TT shots for women aged 15–49 years, with an assumption of full mother/neonate protection at that milestone.

WHAT THIS STUDY ADDS

⇒ This study shows an association between third trimester TT dose and adequate antibody levels in the newborn.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study should serve as foundational research for empirical studies on appropriate timing of TT vaccination in pregnancy.
⇒ Researchers, practioners, and policy makers should undertake cost-effectiveness studies that compare one last trimester TT vaccination to the current regimen of multiple vaccinations throughout pregnancy.

BACKGROUND

Neonatal tetanus has an 80%–100% case fatality[1] but has been eliminated in most of the high-income and middle-income countries through maternal vaccination.[2 3] Every year 34 000 neonates, mostly from low-income and middle-income countries, die from neonatal tetanus.[4 5] In 2018, 45 of 59 priority countries, Uganda inclusive, were validated by WHO as having achieved maternal and neonatal tetanus (MNT) elimination. Relentless implementation of MNT elimination strategies like hygienic childbirth, cord care practices, skilled birth attendance and maternal immunisation programmes need to be maintained and strengthened.[6 7]

Immunisation during pregnancy elicits antitetanus antibodies that protect the mother and the neonates through placental transfer of IgG.[8 9] Antitoxin antibody titres of 0.1–0.15 IU/mL are considered protective[10 11] but neonates born to mothers with suboptimal levels are at risk of death due to neonatal tetanus.[12] Placental transfer of antibodies is a dynamic process beginning around week 17 of gestation,[13 14] with efficiency remaining poor until 32–34 weeks of gestation. Efficiency of placental transfer is dependent on maternal antibody levels,[15] placental function, maternal co-infections, IgG subclass[16] and timing of vaccination. The Advisory Committee on Immunization

Practices (ACIP) recommends that women receive a dose of tetanus toxoid (TT) during the third trimester, between weeks 27 and 36 of gestation in order to provide adequate protection to neonates.[17] Vaccination during the third trimester provides the highest level of transferable antibodies to the neonates. Although WHO does not recommend routine adult booster vaccination for tetanus after completion of childhood vaccination series, many countries including Uganda continue to provide up to five routine booster vaccinations to females of reproductive age (15–49 years).[18] However, this means that mothers receive vaccination before they are pregnant, and in their early pregnancy, often at the first antenatal care (ANC) contact, periods at which the placenta may not be able to transfer protective antibodies to the fetus adequately.[15] Equally, prevalent maternal poor nutrition and infectious diseases burden may synergistically affect vaccine efficacy. We aimed to determine the prevalence of and factors associated with protective tetanus antibodies among newborns at Kawempe National Referral Hospital (KNRH).

MATERIALS AND METHODS

Study design and setting

We conducted a cross-sectional study at KNRH from 1 February to 31 March 2020. KNRH is a teaching hospital for Makerere University School of Medicine. Specimen processing and experiments were performed at the Immunology Laboratory of the Department of Immunology and Molecular Biology, Makerere University College of Health Sciences.

Study setting

Uganda is one of the countries that administers booster TT/tetanus diphtheria (TD) doses for girls and women of reproductive age (15–49 years)[18] and TT/TD remains a mandatory vaccine given to all pregnant women attending ANC visits. KNRH is a level 5 hospital which has delivery rooms and operating theatres. Mothers in labour are triaged at admission and only mothers in active labour are admitted in the delivery rooms. Those that needed emergency caesarean sections are transferred to theatre for surgery. The hospital is about 6.4 km from the central business district. The hospital is open 24 hours, 7 days a week. An average of 70–100 mothers are delivered daily and 30 000 babies annually with a caesarean section rate of 22%.[19] The mothers who deliver within this labour suite are often referred from lower-level facilities due to complicated/high-risk pregnancies or difficult deliveries.

Sample size and sampling

We calculated a sample size of 293 mother-baby pairs using the formula for sample size of a single proportion at a 5% level of significance. We assumed that 74.4% of babies had protective tetanus antibodies basing on a study from Nigeria.[20] We approached every fifth mother recorded in the vertical maternity register for enrolment until sample size was reached. The first participant was chosen randomly from the first five mothers registered that day.

Eligibility criteria

The study enrolled mothers and their newborns delivered at KNRH who consented to study activities during the period of the study. We excluded all babies born before arrival to KNRH, as they already had their umbilical cords ligated and placentae detached. We also excluded mothers admitted in second stage of labour, mothers with intrauterine fetal deaths, mothers too sick to consent and mothers with significant mental disabilities.

Blood sample processing

Two millilitres of venous or cord blood was collected from the mothers and newborns at delivery. To collect the cord blood, the umbilical cord was clamped immediately after delivery of the baby and a needle was used by the obstetrician to collect the blood from the umbilicus. Blood was centrifuged at 1500× g for 15 min and two 0.5 mL aliquots made and stored frozen at −20°C until analysed.

Questionnaire administration

An interviewer-administered questionnaire was used to collect factors associated with maternal transfer of protective antitetanus antibodies, including sociodemographic characteristics of the mother, obstetric, neonatal factors, history of TD vaccination.

Antibody titration

Antitetanus antibody titres were determined using a commercial ELISA kit (MyBioSource, USA catalogue # MBS494626) following manufacturer's instructions. Serum samples were assayed in duplicate, 100 µL/well and at 1:100 dilution. Plates were washed on an ELx50 plate washer (BioTek Instruments) while the plates were read on a SpectraMax Microplate Reader (Molecular Devices). All reagents and plates were supplied with the commercial kit. Mean optical densities (ODs) of the five standard samples were used to generate standard curves for each plate and mean ODs minus background of each test serum was used to determine the antibody titres of mothers and babies. The results were expressed as IU/mL.

Study variables

The primary outcome was the presence of a protetive level of anti-TT antibodies in umbilical blood, categorised as yes (≥ 0.1 IU/mL) and no (<0.1 IU/mL). The explanatory variables included factors that were associated with transfer of protective antibodies. Sociodemographic factors were age, level of education, marital status, history of previous vaccination. Medical factors were chronic illnesses such as HIV, hypertension (blood pressure >140/90 mm Hg), febrile illness (body temperature >37.5°C), diabetes, malaria in pregnancy. Obstetric factors included parity, gestational age, gestation age at vaccination, gestation age at delivery, birth weight,

number of antenatal clinics attended. Biomedical factors were maternal tetanus antibody levels.

Data analysis

Data were summarised using means and SD for normally distributed data and median and IQR for skewed data. The prevalence of protective tetanus antibodies was determined as the proportion of newborns with protective anti-TT antibodies (>0.1 IU/mL). Data were entered into Epidata V.3.1 and exported to Stata V.17.0 for analysis. Factors associated with protective tetanus antibodies among newborns were analysed by generalised linear regression model for the Poisson family, with a log link and robust variance estimation. The strength of the association of the factors with levels of protective levels of anti-TT antibodies was determined from the crude prevalence ratio (cPR) from the regression analyses. The cPR was adjusted to adjusted prevalence ratio (aPR) by controlling for other independent variables in the regression re-analyses. We included all factors that are known to affect the anti-TT antibody levels in the newborn in the final model, based on biological plausibility.

Patient and public involvement

Patients and the public were not involved in the design and conduct of the study. Participants were individually informed of their TT antibody titres. A policy brief was prepared and shared with the Uganda National Expanded Programme on Immunisation, the body responsible for planning management of immunisations in the country.

RESULTS

Characteristic of study participants

We examined serum samples from 293 mother-baby pairs. Majority (185/293, 62.8%) of the mothers were aged 21–30 years with a median age of 25 years (IQR 21–30). More than 60% of mothers were at two or more parity and 22.9% (67/293) were at three or more parity. A half of the mothers had a secondary level of education (156/293, 53.2%). Almost all maternal participants (283/293, 96.6%) reported ever receiving a TT vaccine shot in their lifetime. Less than a half (123/293, 42%) had four or more ANC contacts during the current pregnancy despite WHO recommending eight contacts. HIV and diabetes occurred at a prevalence of 10.3% (30/293) and 2.44 (7/293), respectively among the mothers. Majority of the mothers (58.2%) did not have a source of income but close to 90% declared that they were married. The median birth weight was 3.2 kg (IQR 2.85–3.5) and 77% (225/293) of the neonates were born at term. Further characteristics are shown in table 1 and table 2.

Protective antitetanus antibodies among newborns

The prevalence of protective levels of antitetanus antibody titres among neonates was 258/293 (88.1%: (95% CI 83.8 to 91.3)). The mean (SD) antibody titres were 3.37±2.32 IU/mL.

Table 1 Sociodemographic characteristics of study participants

Variable	N=293	Per cent (%)
Age (years)		
<21	48	16.70
21–30	185	62.50
>30	60	20.80
Religion		
Catholic	124	42.30
Muslim	55	18.80
Anglican	61	20.80
Protestant	48	16.40
Other	5	1.70
Marital status		
Married	263	89.80
Single	11	3.80
Others	19	6.50
Education		
None	6	1.70
Primary	92	31.10
Secondary	156	53.40
Tertiary	39	13.90
Income source		
Yes	122	41.80
No	170	58.20
Parity		
1	115	39.10
2–3	111	38.00
>3	67	22.90
Gestation at first ANC		
≤12 weeks	34	11.60
>12 weeks	259	88.40
ANC visits		
1	36	12.30
2–3	134	45.70
4	75	25.60
>4	48	16.40
Febrile illness		
Yes	54	18.40
No	239	81.60
HIV status		
Positive	30	10.30
Negative	262	89.70
Per Vaginal bleeding		
Yes	19	6.50
No	274	93.50
Hypertension		

Continued

Table 1 Continued

Variable	N=293	Per cent (%)
Yes	18	6.14
No	275	93.86
Diabetes		
Yes	7	2.44
No	280	97.56
Gestation at delivery		
<37	67	22.87
≥37	226	77.13
Birth weight		
<2.5	40	13.65
>2.5	253	86.35

ANC, antenatal care.

Factors associated with adequate levels of protective antibodies among newborns

Mothers with antitetanus antibodies ≥0.1 IU/mL were at 3 times as likely to have newborns with protective antibody titres (aPR 3.1, 95% CI 1.5 to 6.4) compared with mothers with antibodies <0.1 IU/mL. Newborns born to mothers who received their last TT/TD dose at 28 or more weeks of gestation were 1.1 times as likely to have protective antibody titres as newborns born to mothers who received their last TT/TD dose before 28 weeks of gestation (aPR 1.1, 95% CI 1.0 to 1.3). Newborns whose mothers received two or more TT/TD doses during current pregnancy were 1.1 times as likely to have protective antibody titres as newborns whose mothers received one or no TT/TD (table 3) (aPR 1.1, 95% CI 1.0 to 1.2). However, our results show no association of previous history of TD doses (before current pregnancy) with protective antibody levels among newborns irrespective of whether ≥5 (aPR 0.94, 95% CI 0.85 to 1.0) doses had been received before the current pregnancy. We observed comparable antitetanus antibody levels between neonates born to mothers aged 20 years and below and those of above 30 years, although neonates of mothers aged 21–30 yearsshowed a slightly elevated levels than both groups. The results of the findings are shown in table 3.

DISCUSSION

We found a high (88%) prevalence of protective antibody titres among neonates born at KNRH. Uganda is one of the countries that administers booster TT/TD doses for girls and women of reproductive age (15–49 years)[18] and TT/TD remains a mandatory vaccine given to all pregnant women attending ANC visits. This could explain the high prevalence of protective antibody titres among newborns in our study. This is supported by the fact that higher maternal antitetanus antibody titres were associated with presence of protective antibody titres among

Table 2 Tetanus diphtheria (TD) vaccination characteristics among mother-infant pairs in Uganda

Variable	N=293	Per cent (%)
Ever received TD		
Yes	283	96.6
No	10	3.41
TD doses		
0	9	3.07
1	94	32.08
2	165	56.31
3	22	7.51
4	3	1.02
TD dose interval (weeks)		
<3	104	35.70
3–4	105	36.10
5–8	59	20.30
9–12	19	6.50
>12	4	1.40
Received TD before pregnancy		
Yes	201	73.90
No	71	26.10
TD doses before pregnancy		
0	70	24.40
1	35	12.20
2	62	21.60
3	30	10.50
4	33	11.50
5	26	9.10
>5	31	10.80
Gestation at last TD dose		
<28	76	26.12
≥28	162	73.88

newborns. This finding has also been reported by Sangpetchsong *et al*, who show that mothers who had protective levels of tetanus antitoxin transferred protection to almost all of the newborns (97%–100%) and levels transferred correlated with maternal titres.[21 22]

Poor, inconsistent and/or late ANC attendance, sometimes past 28 weeks of gestation, is prevalent in Uganda,[23] especially in mothers from low-income settings who deliver in public health facilities like KNRH where this study was conducted. Although the ACIP recommends a TD shot to pregnant mothers at 27–36 weeks of gestation irrespective of their past vaccination status,[1] in practice expectant mothers in Uganda are given a TD shot at their earliest ANC visit, sometimes earlier than 12 weeks for fear that they may never return for additional ANC contacts. In the event that they return, a booster TD shot is administered again, sometimes completing the ideal two doses earlier than the recommended 27–36 weeks when the

Table 3 Factors associated with adequate levels of protective antitetanus antibodies among newborns

Variable	Crude PR	Adjusted PR	95% CI	P value
Maternal TT antibodies (IU/mL)				
<0.1	1	1		
≥0.1	3.3 (1.6–7.0)	3.1	1.5 to 6.4	0.002
Gestation at first ANC visit				
≤12 weeks	1	1		
>12 weeks	1.3 (1.0–1.6)	1.2	1.0 to 1.5	0.030
Gestation at last TD dose				
<28 weeks	1	1		
≥28 weeks	1.3 (1.1–1.5)	1.1	1.0 to 1.3	0.034
TT/TD doses before current pregnancy				
<5 doses	1	1		
≥5 doses	0.94 (0.84–1.1)	0.94	0.85 to 1.0	0.244
TT/TD doses during current pregnancy				
0–1	1	1		
2	1.2 (1.1–1.3)	1.1	1.0 to 1.2	0.025
3–4	1.3 (1.2–1.4)	1.1	1.0 to 1.2	0.004
Maternal age (years)				
≤20	1	1		
21–30	1.1 (0.97–1.3)	1.1	0.95 to 1.2	0.259
>30	1.0 (0.88–1.2)	1.0	0.86 to 1.2	0.865
Birth weight (kg)				
≥2.5	1	1		
<2.5	0.80 (0.66–0.97)	0.86	0.74 to 1.0	0.059
HIV				
No	1	1		
Yes	0.94 (0.80–1.1)	1.0	0.92 to 1.17	0.555
High blood pressure (>140/90 mm Hg)				
No	1	1		
Yes	1.0 (0.85–1.2)	1.0	0.92 to 1.2	0.608
Febrile (>37.5°C)				
No	1	1		
Yes	1.0 (0.91–1.1)	1.0	0.91 to 1.1	0.936

ANC, antenatal care; PR, prevalence ratio; TD, tetanus diphtheria; TT, tetanus toxoid.

placenta is not well developed to ensure adequate transfer of antibodies to the fetus.[14] Our study showed association between a TD dose at ≥28 weeks and protective levels of anti-TT antibodies among neonates, although the effect seen here was small. Nonetheless the result supports the ACIP recommendation of timing of TD shots in expectant mothers together with recommendations of several other similar studies.[24] This finding is supported by data from another similar study in Texas, USA, which demonstrated that neonates of mothers immunised preconception or in early pregnancy had insufficient antibodies to protect against tetanus infection.[25] Unfortunately, the Ministry of Health in Uganda has not yet adopted the ACIP guidelines as of 2021.

Our finding of comparable TD vaccine-specific antibody responses between HIV-infected and HIV-uninfected counterparts agrees with other studies which have also found protection rates of 80%–100% among HIV-infected TD vaccine recipients.[26] Of surprise, however was our disagreement with another Ugandan study conducted among young males seeking safe male circumcision that found HIV-infected TD recipients had elicited poorer tetanus antibody responses.[27] The difference between the genders enrolled in both studies

perhaps might account for the observed differences. The fact that in Uganda TT/TD booster doses are administered to females as early as 15 years of age, but not to their male counterparts might also explain the discrepancy.

Our study demonstrated that vaccination received before the current pregnancy was not protective, regardless of the number of historical doses received. This is a very important finding in Uganda's setting because it is widely presumed that completion of the immunisation schedule of 5 TT/TD doses between 15 and 49 years offers lifelong protection, which may not be the case in the context of our results. Our study findings agree with the most recent (2020) published ACIP general recommendation that pregnant women should receive one dose of TD during each pregnancy, irrespective of their history of previously receiving the vaccine.[1] Nonetheless, in our context of Uganda, pregestation TD doses for the young girls and mothers may play a role in increasing the odds of boosting vaccine responses and the transplacental transfer of tetanus antibodies to the newborn in those who receive TT/TD vaccination during pregnancy.

Low birth weight was found to have an effect on levels of antitetanus antibodies supporting another West African study that also concluded that babies with low birth weight or those born prematurely[28] tended to have lower antibody levels compared with their normal weight counterparts. This observation in part could be as a result of impaired maternal-to-neonate antibody transfer due to the fact that placental transfer of IgG occurs in an exponential fashion as pregnancy progresses, with minimal transfer in the first trimester and the highest transfer in the third trimester.[8 29 30] Okoko *et al* demonstrated lower transplacental transport of IgG antibodies in the preterm neonates compared with term neonates.[28] The nutritional status of the mothers could play a role in their immunological responses to vaccines, including TT/TD and subsequent transfer of antibodies to neonates,[31] although in this study we never established the nutritional status of the mothers.

It was reassuring to find that regardless of maternal age, neonates had comparable antibodies against tetanus. It is known that performance of one's immune system diminishes with age, including responses to adulthood vaccination, a situation that would impact umbilical maternal-to-neonate transfer of antibodies. Kugelman *et al* for instance reported an inverse relationship between maternal age with transfer of BNT162b2 messenger RNA COVID-19 vaccine-specific antibodies to neonates, with an unprecendented 2.7% reduction per 1 year increment in maternal age.[32] This age-specific effect on maternal antibody levels, their transfer to and subsequently neonatal tetanus antibodies seems to be an exception as evidenced by our data. Our findings are supported by Oguti *et al*, who equally found no maternal-specific differences in anti-TD/TT antibodies or in the rate of anti-TT/TD antibody level half-life in mothers or their infants.[33]

LIMITATIONS

Gestational age was difficult to assess reliably in our setting, especially since majority of the mothers did not have a first trimester ultrasound scan. It was hard to determine whether mothers truly had chronic illness like hypertension, diabetes, HIV, kidney disease since most mothers do not routinely go for check-up before pregnancy.

The CI was large due to a low sample size.

CONCLUSIONS

We found a high (93.9%) prevalence of protective levels of tetanus antibodies among mothers, with an 88.1% prevalence of transfer of protective tetanus antibodies to their neonates born at KNRH, Kampala, Uganda. Prevalence of protective levels of antibodies in newborns was associated and correlated with high levels of maternal antibodies, receiving TT/TD vaccine dose within the third trimester, the number of ANC contacts and birth weight of newborn. We also found that previous vaccinations received before the current pregnancy may not be protective to the newborn. Our finding add on the evidence that elicitation of strong antibody titres through booster TT/TD shots during pregnancy will remain a necessary requirement for control and elimination of neonatal tetanus infections as well as mortality.

We therefore recommend more studies with a larger sample size to ascertain the ideal timing for TD immunisation during pregnancy. Also, the notion that accumulate of five or more TD doses accords sufficient subsequent protection against tetanus infection should be discarded, and mothers given TD vaccination at every pregnancy.

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REFERENCES

1 Liang JL, Tiwari T, Moro P, *et al*. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep* 2018;67:1–44.
2 Raza SA, Avan BI. Eliminating maternal and neonatal tetanus and promoting clean delivery practices through disposable clean birth kits. *Front Public Health* 2019;7:339.
3 Roper MH, Vandelaer JH, Gasse FL. Maternal and neonatal tetanus. *Lancet* 2007;370:1947–59.
4 Khan R, Vandelaer J, Yakubu A, *et al*. Maternal and neonatal tetanus elimination: from protecting women and newborns to protecting all. *Int J Womens Health* 2015;7:171–80.
5 Burgoine K, Egiru E, Ikiror J, *et al*. Neonatal tetanus in Eastern Uganda: improved outcome following the implementation of a neonatal tetanus protocol. *Trop Doct* 2020;50:57–62.
6 Njuguna HN, Yusuf N, Raza AA, *et al*. Progress toward maternal and neonatal tetanus elimination — worldwide, 2000–2018. *MMWR Morb Mortal Wkly Rep* 2020;69:515–20.
7 Thwaites CL, Beeching NJ, Newton CR. Maternal and neonatal tetanus. *Lancet* 2015;385:362–70.
8 Wilcox CR, Holder B, Jones CE. Factors affecting the Fcrn-mediated Transplacental transfer of antibodies and implications for vaccination in pregnancy. *Front Immunol* 2017;8:1294.
9 Gill TJ, Repetti CF, Metlay LA, *et al*. Transplacental immunization of the human fetus to tetanus by immunization of the mother. *J Clin Invest* 1983;72:987–96.
10 Blencowe H, Lawn J, Vandelaer J, *et al*. Tetanus Toxoid immunization to reduce mortality from neonatal tetanus. *Int J Epidemiol* 2010;39 Suppl 1(Suppl 1):i102–9.
11 Tapia MD, Pasetti MF, Cuberos L, *et al*. Measurement of tetanus Antitoxin in oral fluid: a tool to conduct Serosurveys. *Pediatr Infect Dis J* 2006;25:819–25.
12 Anh NQ, Hong HA, Nhon TN, *et al*. Tetanus antibodies measured by the toxin binding inhibition test (Tobi) in mothers and children in the neonatal tetanus program in Vietnam. *Dev Biol Stand* 1999;101:247–53.
13 MacDougall DM, Halperin BA, Langley JM, *et al*. Knowledge, attitudes, beliefs, and behaviors of pregnant women approached to participate in a Tdap maternal immunization randomized, controlled trial. *Hum Vaccin Immunother* 2016;12:879–85.
14 Xu Y, Mahmood I, Zhong L, *et al*. Passive Immunoprophylaxis for the protection of the mother and her baby: insights from in vivo models of antibody transport. *J Immunol Res* 2017;2017:7373196.
15 Halperin BA, Morris A, Mackinnon-Cameron D, *et al*. Kinetics of the antibody response to tetanus-diphtheria-Acellular pertussis vaccine in women of childbearing age and postpartum women. *Clin Infect Dis* 2011;53:885–92.
16 Chu HY, Englund JA. Maternal immunization. *Clin Infect Dis* 2014;59:560–8.
17 Updated recommendations for use of tetanus Toxoid, reduced diphtheria Toxoid, and Acellular pertussis vaccine (Tdap) in pregnant women--advisory committee on immunization practices (ACIP), 2012. *MMWR Morb Mortal Wkly Rep* 2013;62:131–5.
18 Slifka AM, Park B, Gao L, *et al*. Incidence of tetanus and diphtheria in relation to adult vaccination schedules. *Clin Infect Dis* 2021;72:285–92.
19 Hughes NJ, Namagembe I, Nakimuli A, *et al*. Decision-to-delivery interval of emergency cesarean section in Uganda: a retrospective cohort study. *BMC Pregnancy Childbirth* 2020;20:324.
20 Bashir MF, Elechi HA, Ashir MG, *et al*. Neonatal tetanus immunity in Nigeria: the effect of HIV infection on serum levels and Transplacental transfer of antibodies. *J Trop Med* 2016;2016:7439605.
21 Gendrel D, Richard-Lenoble D, Massamba MB, *et al*. Placental transfer of tetanus antibodies and protection of the newborn. *J Trop Pediatr* 1990;36:279–82.
22 Sangpetchsong V, Vichaikummart S, Vichitnant A, *et al*. Transfer rate of Transplacental immunity to tetanus from non-immunized and immunized mothers. *Southeast Asian J Trop Med Public Health* 1984;15:275–80.
23 Kawungezi PC, AkiiBua D, Aleni C, *et al*. Attendance and utilization of Antenatal care (ANC) services: multi-center study in Upcountry areas of Uganda. *Open J Prev Med* 2015;5:132–42.
24 Abu-Raya B, Giles ML, Kollmann TR, *et al*. The effect of timing of tetanus-diphtheria-Acellular pertussis vaccine administration in pregnancy on the avidity of pertussis antibodies. *Front Immunol* 2019;10:2423.
25 Healy CM, Rench MA, Baker CJ. Importance of timing of maternal combined tetanus, diphtheria, and Acellular pertussis (Tdap) immunization and protection of young infants. *Clin Infect Dis* 2013;56:539–44.
26 Kroon FP, van Dissel JT, Labadie J, *et al*. Antibody response to diphtheria, tetanus, and Poliomyelitis vaccines in relation to the number of Cd4+ T lymphocytes in adults infected with human immunodeficiency virus. *Clin Infect Dis* 1995;21:1197–203.
27 Makumbi F, Byabagambi J, Muwanika R, *et al*. Prevalence of protective tetanus antibodies and immunological response following tetanus Toxoid vaccination among men seeking medical circumcision services in Uganda. *PLoS One* 2018;13:e0209167.
28 Okoko JB, Wesumperuma HL, Hart CA. The influence of Prematurity and low birthweight on Transplacental antibody transfer in a rural West African population. *Trop Med Int Health* 2001;6:529–34.
29 Palmeira P, Quinello C, Silveira-Lessa AL, *et al*. Igg Placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol* 2012;2012:985646.
30 Simister NE. Placental transport of immunoglobulin G. *Vaccine* 2003;21:3365–9.
31 Obanewa O, Newell M-L. Maternal nutritional status during pregnancy and infant immune response to routine childhood Vaccinations. *Future Virol* 2017;12:525–36.
32 Kugelman N, Nahshon C, Shaked-Mishan P, *et al*. Maternal and neonatal SARS-Cov-2 immunoglobulin G antibody levels at delivery after receipt of the BNT162b2 messenger RNA COVID-19 vaccine during the second trimester of pregnancy. *JAMA Pediatr* 2022;176:290–5.
33 Oguti B, Ali A, Andrews N, *et al*. The half-life of maternal Transplacental antibodies against diphtheria, tetanus, and pertussis in infants: an individual participant data meta-analysis. *Vaccine* 2022;40:450–8.